New Approaches to Managing Spasticity in Children With Cerebral Palsy

CEREBRAL PALSY is the most common childhood physical disability, affecting as many as 1 in 400 children. This nonprogressive disorder of movement and posture is caused by varied congenital, structural, and acquired insults to the central nervous system, generally within the first three years of maturation. Patients show various patterns of spasticity, rigidity, dystonia, tremors, ataxia, weakness, and primitive movement patterns with poor motor control and postural responses. Secondary musculoskeletal complications such as contractures, hip instability, and spinal deformity also impede function. Spasticity, characterized by velocity dependent increase in tonic stretch reflexes and exaggerated tendon jerks, is a major cause of impairment and disability.

Treatment approaches for spasticity in cerebral palsy have traditionally included physical and occupational therapy; the use of oral medications such as diazepam, dantrolene sodium, and baclofen; intramuscular chemical neurolysis with phenol or ethanol; and permanent ablative neurosurgical procedures such as selective dorsal rhizotomy. Physical and occupational therapies have limited effects on spasticity. Oral medications have systemic side effects and limited efficacy, particularly in persons with cerebral palsy. Whereas rhizotomy alleviates spasticity in cerebral palsy, spasticity reduction cannot be titrated, resulting in excessive hypotonia in some patients. The intramuscular administration of botulinum toxin for focal spasticity and continuous intrathecal baclofen infusion for generalized spasticity are useful new techniques for managing this disorder in children with cerebral palsy.

Administering purified, commercially prepared botulinum toxin into a spastic muscle results in a temporary (3 to 6 months) reduction in spasticity. Botulinum toxin acts at the neuromuscular junction, preventing the presynaptic release of acetylcholine, thus resulting in functional denervation. In contrast to phenol or alcohol, botulinum toxin can be given without anesthesia, electrical stimulation is not usually required to locate injection sites, and the procedure is no more painful than administering saline solution. Although botulinum toxin is the most potent biologic neurotoxin known, its use for the treatment of disorders such as dystonia, blepharospasm, strabismus, and spasticity has not been reported to cause serious systemic toxic effects. Compared with the administration of phenol or alcohol, botulinum toxin is less painful and is easier to administer. The medication is more expensive, but this is offset by decreased physician time and the absence of anesthesia costs in some children. Repeated administrations can induce eventual antibody formation and decrease efficacy, but spacing serial injections at least two to three months apart may prevent this problem.

Continuous intrathecal baclofen infusion using a refillable, programmable, implanted pump can reduce upper and lower extremity spasticity in patients with cerebral palsy. Baclofen is a γ-aminobutyric acid agonist acting primarily at the spinal cord level, but it crosses the blood-brain barrier poorly. Oral administration at higher doses may result in serious systemic side effects. Intrathecal infusion results in a substantial increase in cerebrospinal fluid concentrations and a manifold increase in spasticity reduction at about 1/100th the daily oral dosage. Candidates for continuous intrathecal baclofen infusion are identified through clinical examination. Efficacy is determined for a specific patient by an intrathecal trial of a bolus of baclofen given through a spinal needle or intrathecal catheter. If the spasticity responds to the trial bolus, the programmable pump is placed in the subcutaneous fat of the lower abdomen and connected to a catheter extending into the intrathecal space. Subsequently, the infusion rate can be adjusted periodically with the use of a computer-controlled, radiotelemetry programmer.

Continuous intrathecal pump infusion of baclofen is highly effective in reducing generalized spasticity in cerebral palsy. Compared with selective dorsal rhizotomy, the pump offers the advantage of titratable spasticity reduction, making it more suitable for patients with underlying weakness who rely on some degree of spasticity to ambulate or perform transfers. In addition, titrating to a higher dose may possibly allow greater upper extremity spasticity reduction. The pump reservoir requires percutaneous refilling every two to three months, and the pump is easily replaced surgically every four to five years, which is the approximate battery life.

Botulinum toxin is currently being used by many clinicians for spasticity reduction. Intrathecal baclofen infusion is approved by the Food and Drug Administration for the management of spasticity of spinal and cerebral origin in patients aged 4 years and older. When applied appropriately, both treatments appear to be promising adjuncts to other interventions for enhancing function in cerebral palsy.

DUKJIN IM, MD
CRAIG M. McDONALD, MD
Sacramento, California

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New Drugs for Improving Injury Outcome in Spinal Cord Injuries

TRAUMATIC SPINAL CORD INJURY induces the local release of chemical mediators, neurotransmitters, ions, opioids, and chemotactic factors that add chemical and biologic

injury to the original mechanical disruption. Current research is aimed at neutralizing these secondary effects as early as possible after injury to preserve function in undamaged tissue. The administration of high-dose methylprednisolone sodium succinate has been shown to improve the outcome after spinal cord injuries. The use of tirilazad mesylate and GM_1 ganglioside is being studied.

In initial trials, methylprednisolone was not effective in improving the outcome. In the second National Acute Spinal Cord Injury Study (NASCIS II), methylprednisolone was given in a dosage of 30 mg per kg of body weight within 8 hours of injury, followed by the administration of methylprednisolone, 5.4 mg per kg per hour, for 24 hours. This regimen produced significant neurologic improvement on six-month and one-year follow-up tests when compared with placebo. As a result the methylprednisolone protocol has become the standard of care. The beneficial effects of methylprednisolone seem to result not so much from the anti-inflammatory effects seen at much lower doses, but rather from an ability to scavenge free oxygen radicals and to block "lipid peroxidation," a rancidification of the fatty acid chains that make up neuron cell membranes.

The search for steroids with less anti-inflammatory and more antioxidant activity led to a group of compounds retaining the tetracyclic steroid nucleus but being able to profoundly suppress lipid peroxidation. So far their success has been so great that the agents have been given the name "lazeroids" (after Lazarus). The use of the most promising of these, tirilazad mesylate, greatly improved walking ability in cats if given within four hours of injury. At eight hours after injury, tirilazad was no longer effective even at triple the dose.

Third NASCIS Trial

Tirilazad has been included in one of the three treatment arms in the NASCIS III trial. Treatment arm 1 consists of current methylprednisolone treatment; treatment arm 2 consists of the current methylprednisolone treatment extended for two days; and treatment arm 3 consists of the administration of methylprednisolone, 30 mg per kg, followed by tirilazad, 2.5 mg per kg every 6 hours for 24 hours. The study is intended to determine the best time for starting the methylprednisolone regimen, the optimal duration of therapy, and the benefits, if any, of substituting tirilazad mesylate for methylprednisolone after the initial dose.

GM_1 Ganglioside

Unlike methylprednisolone and tirilazad, which can be thought of as "preservative," GM_1 ganglioside is the first seriously studied agent that could be considered "regenerative." When normal GM_1 turnover is blocked by an enzyme (hexosaminidase) deficiency, GM_1-lipid storage disease results (GM_2-lipid storage disease is Tay-Sachs disease). After central nervous system neurons of a cat with GM_1 storage disease were found to have axonal sprouting of most neurons, many GM_1 studies, including a human clinical trial, were undertaken. One study showed that patients receiving GM_1 ganglioside achieved a higher level of functioning than those given a placebo.

Although methylprednisolone, tirilazad, and GM_1 ganglioside are the major agents currently being studied, other agents are being developed. In the future, we can envision paramedics or trained police officers carrying drugs and administering them before a patient is evacuated. In this way, we might see an increase in the percentage of patients with incomplete instead of complete spinal cord injuries.

PETER C. WERNER, MD
San Jose, California

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Management of Suffering in Patients With Severe Burn Injury

BURN INJURIES are a frequent, painful, and often disabling form of trauma. Such trauma is estimated to account for 731,000 of emergency department visits and 60,900 hospital admissions annually in the United States. The quality of burn care over the past few decades has improved dramatically, resulting in a consistent increase in the number of survivors requiring rehabilitation. Three important challenges in the treatment of burn patients remain: pain control, emotional adjustment, and physical rehabilitation.

Pain control is crucial during acute and intensive phases of burn care. The treatment of partial- and full-thickness burns typically requires frequent dressing changes, debridement, and excision and grafting. Burn wound care is often done daily and may cause more pain than sustaining the burn itself. The use of opioid drugs is the most effective treatment of burn pain, and they should be given immediately and aggressively because virtually no opioid addictions occur in burn patients through treatment. The fear of addiction should not interfere with abating suffering through the appropriate use of opioids. Effective strategies for treating background burn pain include using intravenous morphine sulfate, patient-controlled analgesia, or long-acting orally administered opioids (such as time-release morphine or methadone hydrochloride). Procedural pain is more intense and difficult to control. Morphine or hydromorphone hydrochloride given in a bolus is often effective for dressing